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(54) **Intraocular and intraorbital implantable devices for the controlled release of pharmacological agents.**

(57) A series of implants for intraocular and/or intraorbital use are provided which permit the controlled release of pharmacological agents. The implants (10) are substantially circular or part circular, e.g. C-shaped rings and are insertable through incisions (14) made in the eye wall or are sutured around the globe of the eye. The C-shaped rings may be formed from the biodegradable polymers so as to release a drug as the polymer biodegrades or the implant may be in the form of a hollow flexible polymeric cocoon with the drug disposed therewithin for slow release by osmosis.

FIG. 1

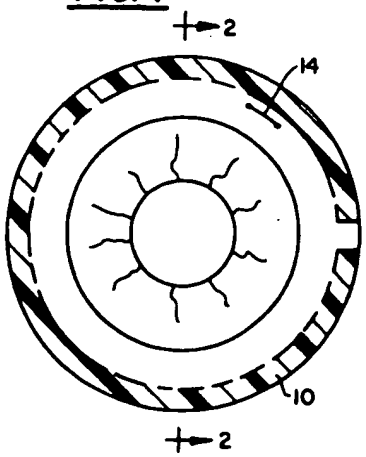
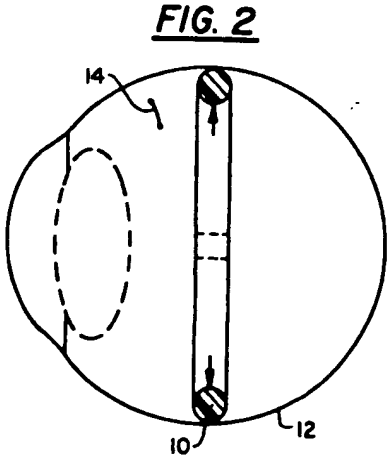


FIG. 2



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The present invention relates to a device for intraocular or intraorbital controlled release of pharmacological agents and a delivery system therefor.

A number of devices have been proposed which permit controlled release of pharmacological agents to various parts of the body and have facilitated dramatic advances in the medical field. Indeed, slow release of insulin from such devices can eliminate the need for repeated insulin injections in the case of a diabetic and the slow release of bactericides can minimise the likelihood of post-operative infection in other cases.

The controlled release of agents for intraocular or intraorbital use would allow optimised therapeutics for AIDS (CMV retinitis), for endophthalmitis (prevention of/cure of bacterial, viral or fungal infections), in proliferative diseases (such as proliferative vitreoretinopathy [PVR], lens epithelium proliferation (secondary cataract), for malignant intraocular tumours and other diseases. In addition, intraorbitally, such a technique would allow control of wound healing (e.g. reduction of scarred tissue volume in glaucoma filtration surgery, retinal detachment surgery (scleral buckling procedure), and strabismus surgery. However to date, devices for the controlled released of appropriate agents for intraocular or intraorbital use have not been developed.

It would therefore be desirable to provide a device for intraocular or intraorbital use which permits the controlled released or slow release of pharmacological agents.

The present invention provides a series of devices or implants for intraocular or intraorbital use which permit the controlled release of pharmacological agents. More particularly, the invention provides in a first aspect a drug containing implant for the controlled release of intraocular and intraorbital pharmacological agents characterised in that the implant is elongate and resiliently predisposed to adopt a curved configuration.

The ends of the elongate insert are free and not joined but they may overlap or abut one another. Alternatively, the implant may be so sized and curved that the ends thereof are separated. All these configurations are collectively referred to herein as "C-shaped rings". The substantially "C-shaped rings" are flexible for insertion through small incisions made in the eye wall or in use are sutured around the globe. The devices are designed to conform with existing surgical techniques (vitrectomy, cataract surgery, penetrating keratoplasty, scleral buckling procedures and glaucoma and strabismus surgery). The implant may release the selected pharmacological agents via biodegradation or by osmosis. The released drug then reaches targeted tissue by diffusion.

Optionally the implant is so sized and curved that when disposed in the orbit external to the globe to provide therapeutic drug release to orbital tissue, ocular muscles, the sclera, and, by diffusion into intraocular tissues first and second ends thereof overlap to serve as a buckle structure; alternatively it may adopt a part circular conformation.

An implant may comprise an implantable device formed from a biodegradable polymer having a drug incorporated therein so that the biodegradation of the polymer releases the drug.

The drug to be delivered by the implantable device may be provided in powder form. A polymer for forming the device may be provided in powder form or liquid form. The powder drug and polymer may be mixed, and said mixture may be processed and shaped into said implant by solvent casting or thermal forming through compression or injection molding techniques.

Covalent bonds may be formed between the polymer and drug molecules so as to create a polymeric drug system such that polymeric degradation releases the drug.

Said drug may be covalently bonded to said polymer via water soluble or hydrolyzable organic links whereby release of the drug occurs by a biodegradation of said organic links.

Said implant may comprise a hollow flexible polymeric cocoon having a drug disposed interiorly of said polymeric cocoon, said drug being diffusible through the walls of said polymeric cocoon into tissue via osmosis.

In a second aspect, the invention provides a drug delivery system for implanting a device into an eye for the controlled release of intraocular and intraorbital pharmacological agents comprising:

an inserter including a cannula (46) having a first end and second end (48) and a passage defined therethrough from said first end to said second end;

a syringe (52) mounted to said first end of said cannula, said syringe including a plunger (56) and a piston (54) extending forwardly therefrom into said passage of said cannula; and

a drug containing implant (44) positioned within said passage forwardly of said piston whereby movement of said piston relative to said cannula ejects said implant from said cannula;

wherein said cannula is adapted to be inserted into an incision in the eye for the ejection of said implant from said cannula to provide therapeutic drug release.

The invention includes such a delivery system or a cannula wherein the said implant is an implant is as described above and which is temporarily straightened wholly or partly from its normal curved configuration in order to be received in said cannula.

The implant may be inserted so as to be positioned intravitreally at the globe's equator so as to release drugs into the vitreous cavity of the eye or so as to be disposed in the angle of the anterior segment.

The implant may be inserted so as to be disposed at the equator of the lens capsular bag of the eye.

Such an implant may be introduced during an extracapsular procedure after removal of the nucleus and cortex to release drugs for preventing lens epithelium proliferation.

The implant may be disposed in the orbit external to the globe to provide therapeutic drug release to orbital tissue, ocular muscles, the sclera, and, by diffusion, into intraocular tissues.

The invention will be illustrated by the following description of preferred embodiments with reference to the drawings, in which:-

FIGURE 1 is a schematic front elevational view showing an implant provided in accordance with the present Invention within the vitreous cavity.

FIGURE 2 is a view taken along line 2-2 of FIGURE 1;

FIGURE 3 is a front elevational view showing an alternate size and location for an implant located in the eye's anterior chamber provided in accordance with the present invention;

FIGURE 4 is a view taken along line 4-4 of FIGURE 3;

FIGURE 5 is a front elevational view showing the implant of the invention disposed at the equator of the lens capsular bag;

FIGURE 6 is a view taken along line 6-6 of FIGURE 5;

FIGURE 7 is a front elevational view showing an alternate location and configuration of the implant provided in accordance with the present invention;

FIGURE 8 is a view taken along line 8-8 of FIGURE 7;

FIGURE 8A is a view similar to FIGURE 8 showing the eye wall deformation when the buckle compresses the eye's equator.

FIGURE 9 is a front elevational view showing yet another implant location for the device of the invention;

FIGURE 10 is a view taken along line 10-10 of FIGURE 9;

FIGURE 11 is a cross-sect3.onal view of a device in accordance with one embodiment of the present invention; and

FIGURE 12 is a cross-sectional view showing an implant inserter provided in accordance with the present design.

Referring to the drawings, the implant of the invention Is shown disposed at various locations in and about a patient's eye. Each disposition of the implant is selected to facilitate optimal drug delivery for the particular treatment being effected and the contemporaneous surgical procedure. For example, referring to FIGURES 1 and 2, intravitreally positioning the "C" ring implant 10 at the equator of the globe 12 is ideal for drug release in the vitreous cavity following vitreoretinal surgery. The implant 10 can be Inserted through an incision as at 14 and is preferably preformed so as to have a diameter slightly larger than the diameter of the vitreous cavity 12. Once inserted, then, the implant 10 will not encroach upon the visual axis and will be maintained in position initially by its resiliency and, within two to four weeks, probably by encapsulation. This device could also be utilized in the treatment of ocular malignancy when loaded with appropriate antimitotic agents such as but not limited to 5-fluorouracil, daunomycin, and others, and for the treatment of CMV retinitis in AIDS patients when loaded with ganciclovir.

Referring to FIGURES 3 and 4, a smaller "C" ring 16 can be made to fit into the angle 18 of the anterior segment 20 following penetrating keratoplasty (corneal transplantation), intraocular cataract surgery, vitrectomy, glaucoma filtering surgery, etc. Again, the implant can be inserted through the surgical incision 22 and could be provided for releasing antibiotics, antimicotics, antimitotics, and/or growth factors.

Referring to FIGURES 5 and 6, another location for a "C" ring 24 provided in accordance with the present invention is at the equator of the lens capsular bag 26. Such a "C" ring 24 can be introduced during extracapsular cataract procedures, after removal of nucleus and cortex, to release drugs preventing lens epithelium proliferation, the cause of posterior capsule opacification (secondary cataract). In the alternative, the "C" ring of the invention could be used as an element for Intraocular lens (IOL) construction or as an IOL coatlng.

By modifylng the ring design slightly as, shown in FIGURES 7 and 8, the "C" ring 28 can be used in the orbit external to the globe 30 (as a buckle) and provide therapeutic drug release to the orbital tissue, ocular muscles, the sclera, and, by diffusion, into intraocular tissues. The ends 32, 34 of ring 28 could be made to overlap or butt and serve as a temporary or permanent buckle (elastic band used in retinal detachment surgery). In the alternative, as shown in FIGURE 8A, the ring 28 could be molded to have a diameter slightly less than the diameter of the globe 30 so that the resiliency of the ring tends to clamp it about the globe and deforming it as for conventional scleral buckling procedure performed with silicone elastic bands wherein the buckle compasses the eye's equator bringing the eye tissue outer coat (sclera) into

contact with the detached retina (inner coat). The ring can also be sutured about the globe to ensure retention of the ting in an appropriate position.

Even further, as shown in FIGURES 9 and 10, positioned under the conjunctiva 36 the "C" ring 38 can release antimitotic agents in order to modulate Would healing and prevent early closure of the filtering bleb in glaucoma surgery and minimize scarring during strabismus and retinal reattachment procedures.

Intraocular insertion of the flexible "C" rings described above can be accomplished by injection with a simple surgical instrument during the contemporaneous procedure (e.g.; vitrectomy, cataract surgery, penetrating keratoplasty, glaucoma filtering surgery) through a small incision made in the eye wall through the conjunctiva as shown, for example, at 14, 22, and 40.

Referring to FIGURE 12, one embodiment of an instrument 42 for implanting the device 44 which includes a cannula 46 for receiving the implant 44 in a straightened configuration. The cannula 46 preferably has a beveled forward end 48 for facilitating insertion of the same into an incision in the eye wall. The cannula 46 further preferably includes a side arm structure 50 for enabling infusion and/or irrigation and aspiration of materials. A modified syringe structure 52 having a piston 54 extending forwardly from the plunger 56 can be employed to eject the implant 44 from the cannula.

In one form of the present invention, the device substrate is made from synthetic biodegradable polymers. The drug is mixed with the polymer (both in fine powder form or with the drug in fine powder form and the polymer in the liquid state) and processed into a "C" ring-shaped implant by solvent casting or by thermoforming through compression or injection molding techniques. Biodegradation of the polymer releases the drug. For a given application site (e.g. intraocular, intraorbital, etc.) release time is a function of the polymer and implant shape selected and can be made to vary from about one week to@about one year.

In another form, the drug is covalently bonded to the polymer backbone via water soluble or hydrolyzable organic links (eg: peptides). Drug release occurs by biodegradation of these links.

In yet another form of the invention, covalent bonds are formed between the polymer and drug moledules to create a polymeric drug system. Polymeric degradation releases the drug.

In a fourth form, the drug is contained in a hollowed flexible polymeric cocoon 58 shaped as a "C" ring (FIGURE 11). The drug 60 diffuses through the wall of the ring into tissue via osmosis.

Biodegradable polymers have been tested subconjunctivally, intraorbitally and intraocularly both in the anterior and the posterior (vitreous cavity) chambers.

Twenty-six of 140 biopolymers tested were found to have adequate physical properties for the fabrication of ocular implants. Three were found intraocularly biocompatible and two of these were selected for the fabrication of implants. Using a 10/90 lactide-glycolide copolymer, biodegradable retinal fixation tacks (biopins) were fabricated and implanted in a series of 30 rabbits. In vitrectomized and non-vitrectomized eyes, the biopins fully biodegraded at 8 and 12 months respectively. As with their metallic counterparts, encapsulation of the biopins develops at approximately 1 month. No foreign body or toxic reaction was observed histologically.

A biodegradable polymer controlled drug release matrix containing 10% 5-FU has been fabricated and tested in vitro. More particularly, using a 50/50 lactide-glycolide copolymer, a 10% 5-FU controlled drug released matrix designed for rapid release was developed. An in vitro technique was developed to assess the pharmacokinetics of the matrix.

Using a 10/90 lactide-glycolide compound, each biopin was designed to release 10ng of drug per hour over a 4 month period. An increased drug rate of 10ug/hr can be achieved with a "C ring" implant. Injectable through a 20ga pars plana incision, this larger implant can be designed to fit the retinal equator thereby avoiding retinal perforation.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not to be limited to the disclosed embodiment, but on the contrary is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

Claims

1. A drug containing implant for the controlled release of intraocular and intraorbital pharmacological agents characterised in that the implant is elongate and resiliently predisposed to adopt a curved configuration.

2. A drug delivery system for implanting a device into an eye for the controlled release of intraocular and intraorbital pharmacological agents comprising:

an inserter including a cannula (46) having a first end and a second end (48) and a passage defined therethrough from said first end to said second end;

a syringe (52) mounted to said first end of said cannula, said syringe including a plunger (56) and a piston (54) extending forwardly

therefrom into said passage of said cannula; and

a drug containing implant (44) positioned within said passage forwardly of said piston whereby movement of said piston relative to said cannula ejects said implant from said cannula;

wherein said cannula is adapted to be inserted into an incision in the eye for the ejection of said implant from said cannula to provide therapeutic drug release.

3. An implant as claimed in Claim 1 or a delivery system as claimed in Claim 2, wherein the implant so sized and curved that when disposed in the orbit external to the globe to provide therapeutic drug release to orbital tissue, ocular muscles, the sclera, and, by diffusion, into intraocular tissue first and second ends thereof overlap to serve as a buckle structure.

4. An implant or a delivery system as claimed in Claim 1 or Claim 2, wherein the implant is so sized and curved that upon release into the eye it adopts a part circular conformation.

5. An implant or a delivery system as claimed in Claim 4, wherein said implantable device is substantially C-shaped once implanted.

6. An implant or delivery system as claimed in any preceding claim, wherein said implant comprises an implantable device formed from a biodegradable polymer having a drug incorporated therein so that the biodegradation of the polymer releases the drug.

7. An implant or a delivery system as claimed in Claim 6, wherein the drug to be delivered by the implantable device is provided in powder form;

a polymer for forming the device is provided in powder form or liquid form;

the powder drug and polymer are mixed; and

said mixture is processed and shaped into said implant by solvent casting or thermal forming through compression or injection molding techniques.

8. An implant or a delivery system as claimed in Claim 6, wherein covalent bonds are formed between the polymer and drug molecules so as to create a polymeric drug system such that polymeric degradation releases the drug.

9. An implant or a delivery system as claimed in Claim 8, wherein said drug is covalently bonded to said polymer via water soluble or hydrolyzable organic links whereby release of the drug occurs by a biodegradation of said organic links.

10. An implant or a delivery system as claimed in Claim 6, wherein said implant comprises a hollow flexible polymeric cocoon having a drug disposed interiorly of said polymeric cocoon, said drug being diffusible through the walls of said polymeric cocoon into tissue via osmosis.

11. A delivery system as claimed in Claim 3, wherein the said implant is an implant in accordance with Claim 1 which is temporarily straightened wholly or partly from its normal curved configuration in order to be received in said cannula.

12. A cannula containing an insert as claimed in Claim 1, wholly or partially straightened from its normal curved configuration to be received in said cannula.

FIG. 1

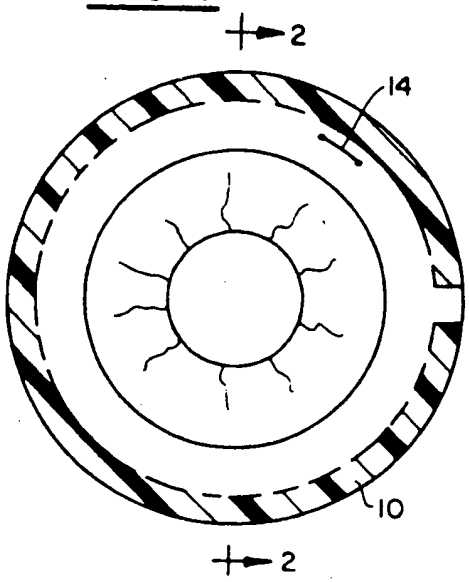


FIG. 2

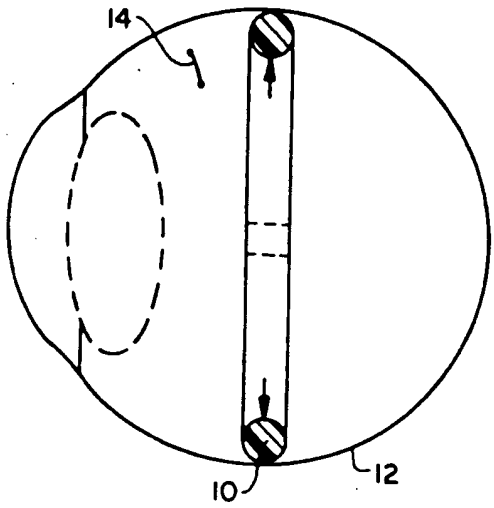


FIG. 3

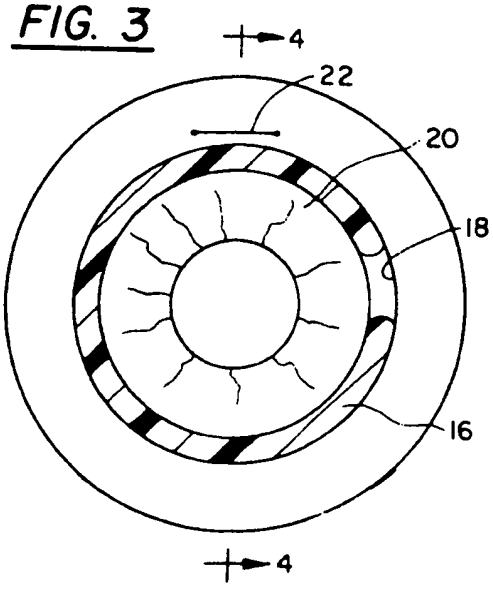
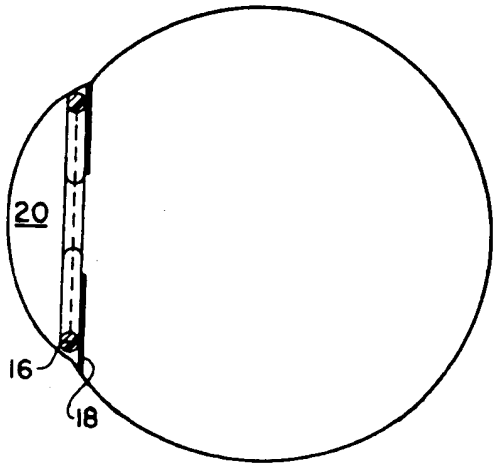


FIG. 4



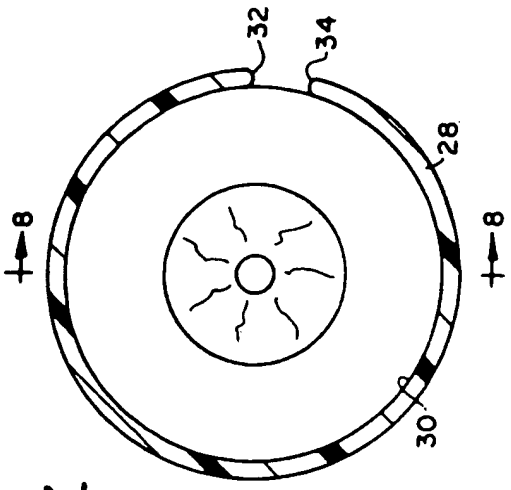


FIG. 7

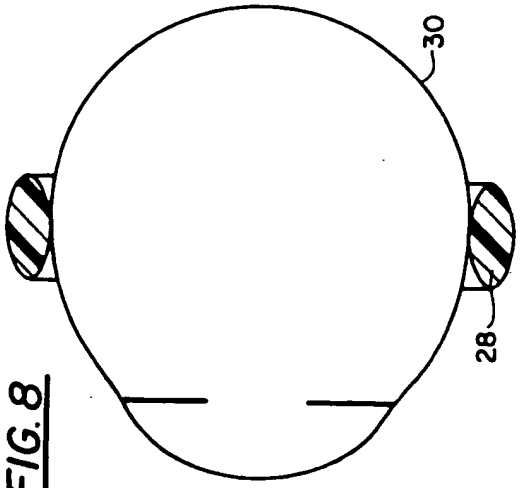


FIG. 8

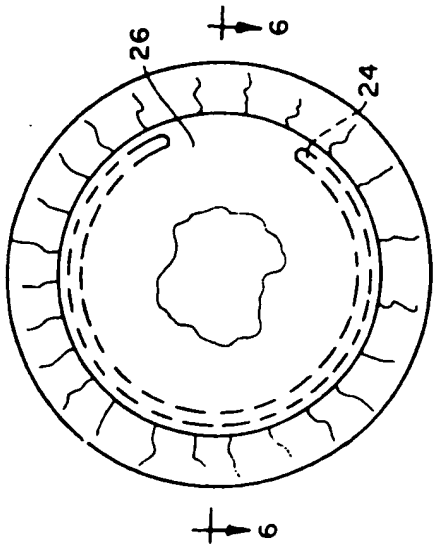


FIG. 5

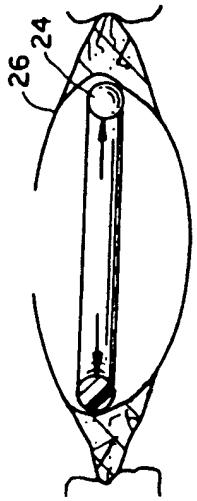


FIG. 6

FIG. 8A

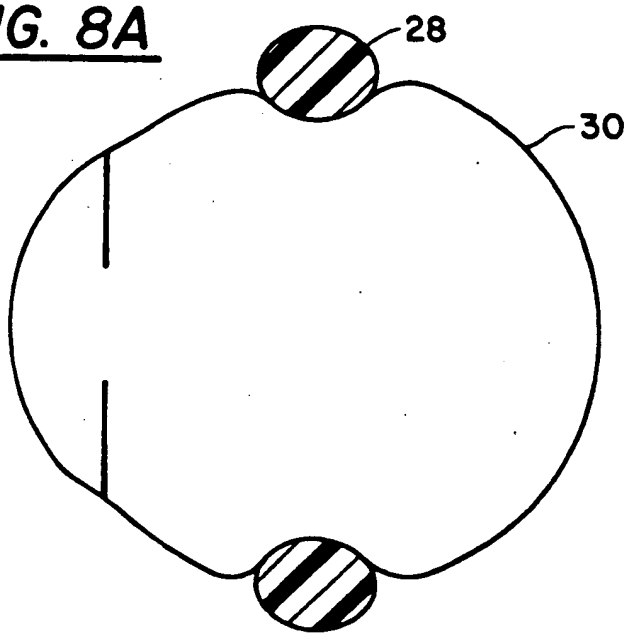


FIG. 8B

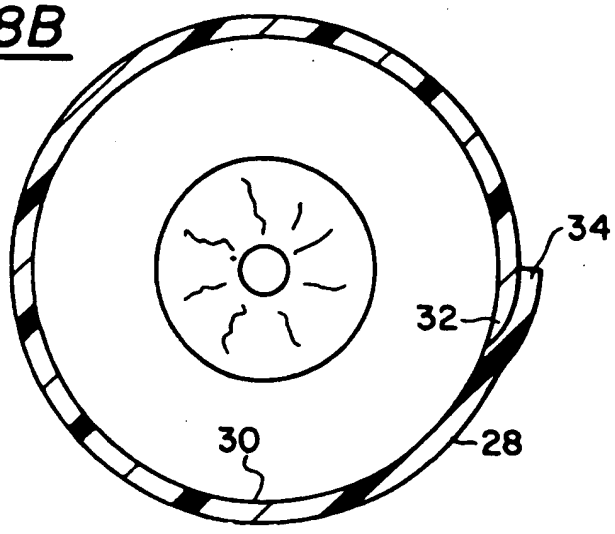


FIG. 9

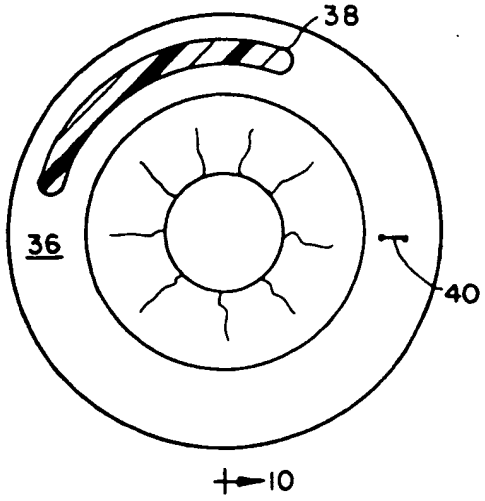
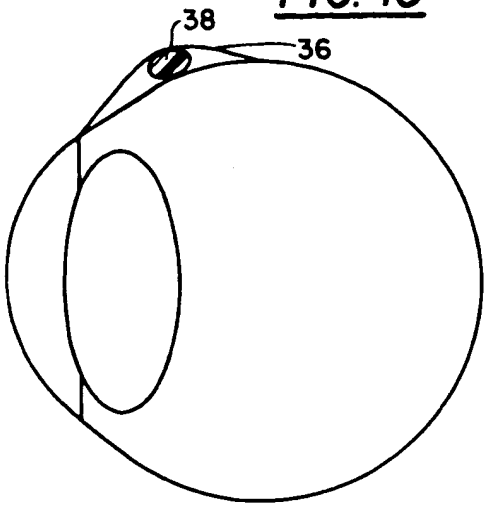


FIG. 10



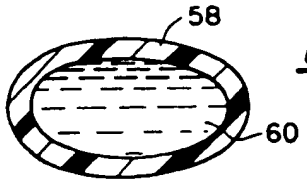
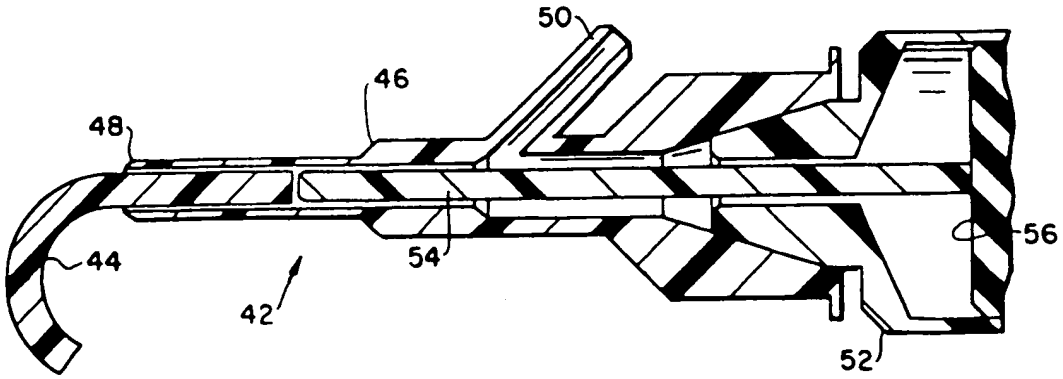


FIG. 11

FIG. 12



European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 31 1112

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	US-A-4 300 557 (REFOJO) * figures 2,5 *	1	A61K9/00 A61F9/00
A	US-A-4 863 457 (LEE) * abstract; figure 4 *	1	
A	US-A-4 955 906 (COGGINS) * abstract; figures 1,3 *	2	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A61K A61F

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	13 JULY 1992	PAPONE F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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